Remarks/Arguments

Claims 39-47, 49-51 are pending in this application. With this amendment, Claims 39-43 have been amended to further clarify what Applicants have always regarded as their invention. Support for polypeptides "comprising polypeptide variants" is found in the specification at, for example, page 57, line 2- page 58, line 2. The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

The rejection is respectfully traversed.

I. Rejections under 35 U.S.C. §101 and §112, first paragraph

Claims 39-51 are newly rejected under 35 U.S.C. 101, for lack of utility, allegedly since the invention is not supported by either a credible, specific and substantial asserted utility or a well established utility (page 2 of Office action). Claims 39-51 are further rejected under 35 U.S.C. 112, first paragraph, allegedly "since the invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention" (page 7-8 of Office action).

Briefly, the Examiner has gone into considerable detail explaining the mechanism of the MLR, also known as the mixed lymphocyte culture (MLC) assay. The Examiner's primary point this rejection is that allegedly "the MLR assay is an artificial *in vitro* system that does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any" (page 3 of the instant Office action). For support, the Examiner quotes Kahan *et al.*, Piccotti *et al.*, Campo *et al.*, and Basic and Clinical Immunology (8^{th} ed.), Ed Stites, Terr and Parslow, and concludes that "the MLR assay, which is recognized for determining histocompatibility, ***does not appear to be predictive of general immune responses in vivo***" (emphasis added- page 5 of the instant Office action). The Examiner further does not agree with the types of controls used in the instant MLR (page 7 of the instant Office action) and also notes that no 'statistical significance' was mentioned. For the reasons outlined below, Applicants respectfully disagree.

A. The Legal Standard for Utility

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

---

[1] *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).
[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.
[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.
[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980)
[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.
[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).
[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.
[8] *Id.*

Furthermore, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it

---

[9] *In re Gazave,* 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967)
[10] *Ibid.*
[11] *In re Langer*, 503 F2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).
[12] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).
[13] *Raytheon v. Roper*, 724 F.2d 951, 956 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).
[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).
[15] 66 Fed. Reg. 1092 (2001).

is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

B. <u>The Data and Documentary Evidence Supporting a Patentable Utility</u>

Applicants submit that, the instant specification, at least in Example 74, page 208, line 27, and the disclosure within the Fong declaration (submitted with Applicants' response of October 25, 2004), describe the mixed lymphocyte reaction (MLR) assay, which is sufficient to establish patentable utility under 35 U.S.C. §101 for the PRO335 polypeptide. The positive result for PRO335 in the MLR assay demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes.

The MLR is a well-established assay for evaluating test compounds, such as the PRO335 polypeptide, for their ability to stimulate T-lymphocyte proliferation *in vitro*, and consequently, for assessing the immune response of an individual. The MLR assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J.E. Coligan, A.M. Kruisbeek, D.H. Marglies, E.M. Shevach, W. Strober, National Institutes

---

[16] M.P.E.P. § 2107.01.
[17] M.P.E.P. § 2107 II (B)(1).

of Health, Published by John Wiley & Sons, Inc., which is referenced in Example 74. In brief, in this method, an immune response results upon mixing T-cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored quantitatively by, for example, following the incorporation of tritiated thymidine during DNA synthesis, or by observing blast formation, or by other methods well known in the art. According to Example 74 of the specification, "[p]ositive increases over control in this assay are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein" (page 209, lines 17). PRO335 (SEQ ID NO: 290) tested positive in this assay, using the described criteria. Example 74 further explains that compounds which stimulate proliferation of lymphocytes in this assay "are useful therapeutically where enhancement of an immune response is beneficial." (page 208, lines 29-30). Accordingly, PRO335 has utility in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable.

In further support of utility based upon the MLR assay, Applicants have submitted (with their Response filed October 25, 2004) the Declaration of Sherman Fong, Ph.D. Dr. Fong is an inventor of the above-identified patent application, and an experienced scientist familiar with the MLR assay, which was used by him and others under his supervision, to test the immune stimulatory or immune inhibitory activity of novel polypeptides discovered in Genentech's Secreted Protein Discovery Initiative project, including PRO335.

The Fong Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Dr. Fong proceeds to explain (paragraph 7 of the Declaration) that dendritic cells are potent antigen-presenting cells that are able to "prime native T cells *in vivo*." Once activated by dendritic cells, the T-cells are capable of interacting with other antigen-presenting cells (B cells and macrophages) to produce additional immune responses from these cells.

As Dr. Fong states, the MLR assay of the present application

> is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously. (Paragraph 8 of the Fong Declaration.)

As Dr. Fong emphasizes, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Costimulation of T cells can induce tumor regression and an antitumor response, both *in vitro* and *in vivo*. Supportive evidence comes from teachings in the art such as Steinman *et al.* (submitted as Exhibit B with the Response filed October 25, 2004) who state that "...**medicine needs therapies that enhance immunity or resistance to infections and tumors**" (page 1, column 1, line 7; emphasis added). It was also well established in the art before the time of the instant filing that T cells recognize human tumor specific antigens (for example, see DeSmet, C. *et al.* (1996) Proc. Nat. Acad. Sci. U.S.A. 93; 7149). Therefore, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be used in immunoadjuvant therapy (with tumor-specific antibodies) for the treatment of tumors (cancer) and could be administered alone or together with other agents to stimulate T cell proliferation/ activation (immune function).

In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. As Dr. Fong explains,

> IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. IL-12 was first identified in just such an MLR [Gubler et al. PNAS 88, 4143 (1991) (Exhibit C)]. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson et al. Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)] They extracted circulating white blood cells carrying one or more markers of melanoma cells, isolated the antigen, and returned them to the patients. Normally patients would not have an immune response to his or her own human antigens. The patients were then treated with different doses of IL-12, an immune stimulant capable of inducing the proliferation of T cells that have been co-stimulated by dendritic cells. Due to the immune stimulatory effect of IL-12, the treatment provided superior results in comparison to earlier work, where patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs), treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response. [Thurner et al. J. Exp. Med. 190 (11), 1669-78 (1999) (Exhibit E)].

Dr. Fong concludes that (paragraph 10):

> It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the polypeptides claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

C. <u>The art recognizes the MLR as an *in vitro* assay useful for identifying compounds with immunmodulatory activity *in vivo*</u>

The Examiner says that allegedly "the MLR assay is an artificial *in vitro* system that does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any" (page 3 of the instant Office action). Applicants respectfully disagree.

Applicants submit that MLR was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. For example, IL-2, a well-known immunostimulant was identified using MLR in Santoli *et al.*, J. Immunol. 137:400-407 (1986); copy enclosed in IDS), and in U.S. Patent Application No. 4,950,647 (column 9, lines 30-36; Table III; copy enclosed in IDS). Based upon its immunostimulatory activity, IL-2 has been demonstrated to have a range of utilities in the treatment of immune deficiencies, as well as in immunotherapy for cancer.

Also, Reddy *et al.* (Infect. Immun. 44:339-343 (1984); copy enclosed in IDS) found that IL-2 augments natural killer cell activity in patients with AIDS. The authors concluded that "consideration of the use of IL-2 as a potential therapeutic agent to modify immune responses in disorders such as AIDS appear warranted" (page 342, col. 2).

Pahwa *et al.* (Proc. Natl. Acad. Sci. USA 86:5069-5073 (1989); copy enclosed in IDS) demonstrated the successful use of therapy with recombinant IL-2 to treat severe combined immunodeficiency disease.

Kirchner *et al.* (Br. J. Clin. Pharmacol. 46:5-10 (1998); copy enclosed in IDS) stated that "[t]he use of recombinant human interleukin-2 (rhIL-2) has been recommended as the best current therapy for advanced renal cell carcinoma" (page 5, col. 1).

Similarly, interleukin 15 (IL-15) was initially identified as a cytokine having a similar structure to IL-2, and was found to be at least as potent and effective as IL-2 in the MLR assay (Grabstein, K.H. *et al.*, Science 264:965-968 (1994); copy enclosed in IDS; see pages 966-967).

Chapoval *et al.* (J. Immunol. 161:6977-6984 (1998); copy enclosed in IDS) further studied the impact of IL-15 as an adjuvant to cancer therapy using cyclophosphamide (CY) in a mouse lung tumor model. The authors noted that it had previously been shown that IL-15 prolonged survival of lymphoma-bearing mice, and suppressed pulmonary metastases induced by injection of sarcoma cells (page 6977, col. 1). In their study, Chapoval *et al.* found that IL-15 significantly increased the rate of cures to 32%, as compared to 6.7% with CY alone (page 6981, col. 2).

Another immunostimulant, interleukin 21 (IL-21) was found to enhance the proliferation of T cells in an MLR assay (Kasaian, M.T. *et al.*, Immunity 16:559-569 (2002); copy enclosed in IDS; see page 565 and Figure 7A).

In a more recent study, Ma *et al.* (J. Immunol. 171:608-615 (2003); copy enclosed in IDS) found that "IL-21 stimulates potent prophylactic and therapeutic immunity that leads to the cure of tumors" (page 608, col. 2). In particular, the authors concluded that "IL-21 alone has the unique potential to prevent or cure poorly immunogenic B16 melanoma tumors" (page 614, col. 1).

Applicants note that MLR studies are not limited to the measurement of the activity of cytokines alone. For instance, the growth factor, granulocyte macrophage colony-stimulating factor (GM-CSF) was identified as a macrophage factor responsible for mediating the enhancement of the MLR by macrophages (Naito, K. *et al.*, J. Immunol. 142:1834-1839 (1989); copy enclosed in IDS) by an MLR-like assay.

In another study, based upon its immunostimulatory activity, GM-CSF was used therapeutically to augment the healing of mucosal and epidermal injury, enhance antimicrobial vaccine efficiency, and to boost host defenses against established infections and cancer (Tarr, P.E, Med. Oncol. 13:133-140 (1996); copy enclosed in IDS; see page 133, col. 1). In particular, Tarr *et al.* disclose that "[i]nitial studies in humans using GM-CSF as adjunctive treatment in disseminated fungal or leishmanial infections, and central nervous system toxoplasmosis in AIDS patients, have already demonstrated encouraging results" (page 135, col. 1). GM-CSF was found to augment antibody responses to immunosuppressed patients to hepatitis B vaccination (page 136, col. 1-col. 2). GM-CSF is used in cancer immunotherapy to expand the population of dendritic cells before reinfusion into the patient (page 136, col. 2).

In yet another study, Gennari *et al.* (Annals of Surgery, 220:68-76 (1994); copy enclosed in IDS) studied the effects of GM-CSF in two clinically relevant models of infection, the susceptibility of transfused and burned mice to gut origin sepsis, and the resistance of mice to bacterial peritonitis after cecal ligation and puncture (page 74, col. 1). The authors found that the mice had a significantly improved survival rate when treated with GM-CSF in both cases (page 72), with the observed therapeutic effects resulting from stimulation of increased production of white blood cells (page 74, col. 2).

In addition, Ma *et al.* (referenced earlier) noted that GM-CSF-based cancer vaccines protect mice from developing B16 melanoma tumors when given prophylactically (page 614, col. 1).

In another study, the glycolipid, alpha-galactosylceramide (α-GalCer) was demonstrated to enhance the T-cell response in an MLR assay by 25-73% (Patterson, S. *et al.*, J. Immunol. 175:5087-5094 (2005); copy enclosed in IDS; see page 5089, col. 2).

In an earlier study, Toura *et al.* (J. Immunol. 163:2387-2391 (1999); copy enclosed in IDS) disclosed that the "[i]njection of α-GalCer inhibits tumor metastasis almost completely in the liver or lung" (page 2387, col. 2). Toura *et al.* found that dendritic cells pulsed with α-GalCer are able to induce antitumor activity *in vivo* within 24 hours after cell transfer (page 2390, col. 2).

In a recent study, the taxanes, paclitaxel and docetaxel were both found to enhance MLR values, with docetaxel demonstrating a more pronounced effect on enhancing MLR (Tsavaris *et*

al., Br. J. Cancer 87:21-27 (2002); copy enclosed in IDS). Both taxane compounds were previously demonstrated to have immunostimulatory effects against neoplasms.

In one study, an extract from the herbal plant *Echium amoenum* (borage) was demonstrated to have a stimulatory effect in the MLR assay (Amirghofran, Z. *et al.*, Irn. J. Med. Sci. 25:119-124, (2000); copy enclosed in IDS).

In a further study, *Echium amoenum*, which is traditionally used for the treatment of infectious diseases, in an extract comparable to that used in the MLR assay was later proven to have an antibacterial effect on *Staphylococcus aureus* (Abolhassani, M., Brazilian Journal of Infectious Diseases 8:382-385, (2004); copy enclosed in IDS).

The MLR assay and its use in identifying immunostimulatory molecules is not restricted to peer-reviewed journals alone. The Examiner's attention is respectfully directed to U.S. Patent No. 5,817,306, filed June 7, 1995 (copy enclosed in IDS). This patent contains claims to methods for treating graft versus host disease using IL-1 receptor antagonists. The specification explains that the effectiveness of IL-1 receptor antagonists in graft versus host disease may be determined by MLR assays. In particular, U.S. Patent No. 5,817,306 states, "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. **The results obtained from these assays are generally predictive of their *in vivo* effectiveness.**" (Column 12, lines 36-41; emphasis added).

The Examiner's attention is further directed to U.S. Patent No. 5,801,193, filed April 15, 1997 (copy enclosed in IDS), which states that "[t]he **MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity.**" (Column 8, lines 8-10, emphasis added).

Applicants further direct the Examiner's attention to U.S. Patent No. 5,958,403, filed July 11, 1994 (copy enclosed in IDS), which describes DNA constructs encoding immunosuppressive proteins for use in the prevention of graft rejection. While U.S. Patent No. 5,958,403 does report results of tests in mouse models of graft vs. host disease, it states that "**[u]seful constructs are also those which provide a mixed lymphocyte reaction (MLR) by decreasing proliferation by 20%**, more preferably 40%, and most preferably, by 60% relative to control cells not expressing the transgene." (Column 6, lines 16-19; emphasis added).

Finally, the Examiner's attention is respectfully directed to U.S. Patent No. 5,648,376, filed January 19, 1995 (copy enclosed in IDS), which states that "[a] measure of immunosuppression that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Column 11, lines 24-26).

Applicants further note that a positive result as a stimulator in the MLR assay is also characteristic of molecules which have known *in vivo* utilities in the treatment of disorders for which stimulation of an immune response is desirable. For example, as discussed above IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay (Gubler *et al.*, PNAS 88:4143 (1991) (submitted as Exhibit C in Applicants' Response filed October 25, 2004). In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of an approach relying on the immune stimulatory activity of IL-12 for the treatment of melanoma. Peterson *et al.*, J. Clin. Oncol. 21:2342-2348 (2003) (submitted as Exhibit D in Applicants' Response filed October 24, 2005).

Thus, **the art as a whole, at the time of filing of the application, clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomostimulatory compounds and that the positive result as a stimulator in the MLR assay is widely accepted as a valid indication of therapeutic use in the treatment of disease conditions, including irradication of tumors.** Applicants note that Dr. Fong's conclusions are consistent with what is accepted in the art. Accordingly, the positive results obtained in the MLR assay clearly establishes an immunostimulatory utility (or suppressive utility, depending on the MLR result) for the polypeptides claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose. Therefore, based on the art's teachings about the immunostimulatory activity of molecules, as a result of a positive MLR assay, would provide sufficient correlation to one skilled in the art, such that they would use the identified compounds in the treatment of disorders for which stimulation of the immune system is beneficial, such as viral or bacterial infections, immune deficiencies, or tumor/cancer treatments.

D. The results of the MLR assay are meaningful

The Examiner has rejected the controls used in the instant MLR assay saying, "there are several controls which the art recognizes as being ***essential*** for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities" (emphasis added- page 7 of the instant Office action). Applicants respectfully disagree.

This rejection indicates that there is a misunderstanding of the state of the art. Applicants submit that these controls (that the Examiner cites above) were only needed for the purpose of evaluating the properties of the stimulator cells. As shown, for example, in Figure 16-4 of "Basic and Clinical Immunology," made of record by the Examiner in the Office Action mailed with instant Office action, the comparisons of the test to mismatched (maximum response) and autologous (background) controls allow one to determine the degree of HLA class II antigen similarity between the stimulator cells and the responder cells. Such determinations, however, are not required for the MLR assay of Example 74, and thus these controls are not "essential".

The purpose of the assay disclosed in the instant specification, as discussed above, is to characterize not the stimulator cells, but the test proteins, such as PRO335. The precise extent to which the stimulator cells stimulate the responder cells is not significant; on the other hand, what matters is the degree to which the test protein enhances this response. The extent to which the test protein enhances the response of the T cells is measured by comparison to a negative control reaction, which uses either cell culture medium, or a non immunomodulatory molecule, CD4-IgG, as a negative control. Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required. Further, the protocols described in the instant specification are consistent with those accepted in the art. For example, U.S. Patent No. 4,950,647, which demonstrated the immunoenhancing activity of the compound 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one using the MLR assay, did not disclose the use of any additional controls beyond those disclosed in the instant application.

The Examiner further noted that "the specification states that "positive increases over control are considered positive," however, this does not indicate that ***statistical significance*** must

occur for determination of a positive result in the assay" (emphasis added- page 7 of the instant Office action). Applicants respectfully disagree.

Applicants respectfully submit that these remarks are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a drug based on the immunoenhancer activity of PRO335, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new immunoenhancer drug, will indeed ask for actual numerical data, statistical analysis, and other specific information before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. Indeed, in *Nelson v. Bowler,* the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to the instant utility as well. The identification of a compound as an immunoenhacer should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

The MLR assay described herein is a comparative one (increases of greater than or equal to 180% is preferred), meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. Useful information is obtained when a relative differences are observed, and this is routine in biological testing. All that is important for utility is that the difference is significant. And Applicants expressly assert that the observed difference for PRO335 is significant (this point is further discussed below based on U.S. Patent No. 4,950,647). For instance, Example 74 of the specification makes clear the standard to be used to determine whether a positive result in the MLR assay is significant, stating that "[p]ositive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred and that PRO335 tested positive in this assay. However, any value greater than control indicates a stimulatory effect for the test protein" (page 203, line 27). Therefore, this disclosure clearly meets the standard for statistical significance. The Examiner seems to focus on exactly how much higher (*i.e.,* requiring Applicants to provide "relative or absolute levels" and statistical analyses), but Applicants

submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful.

Applicants further submit that the term "positive increases over control" would readily be understood by one skilled in the art. For instance, the Examiner's attention is directed to U.S. Patent No. 4,950,647 (copy enclosed in instant IDS), which claims immunoenhancing compositions comprising the compound 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one. The immunoenhancing activity of the claimed compound was determined in part by the use of the MLR assay, as shown in Example IV (column 13, lines 20-37). The claimed compound increased the response in the MLR, with a maximum increase of 191% as compared to control, as shown in Table VII. IL-2 showed a similar level of stimulation of the MLR (with a maximum of 200% as compared to control) as shown in Table III. Thus this patent supports the threshold of 180% described in the instant specification as showing significant stimulatory activity. Given that 6-Amino(2-deoxy-alpha-D-erythro-petofuranosyl)imidazo[4,5,-C] pyridine-4-one was identified as an immunostimulatory compound based upon a reported increase in the MLR assay of 191% as compared to control, the activity for PRO335 of greater than or equal to 180% as compared to control clearly meets the standard accepted in the art as demonstrating patentable utility.

Therefore, this rejection requiring allegedly essential controls and statistical data are not appropriate, as relevant even from the art, and should be withdrawn.

D. A *prima facie* case of lack of utility has not been established

The Examiner also cites several references to show that PRO335 does not have utility based on its positive results in the MLR assay.

For instance, the Examiner cites a reference, Basic and Clinical Immunology (8^{th} ed.), Ed Stites, Terr and Parslow (made of record by the Examiner in the instant Office Action mailed May 30, 2006), and generally concludes that "the MLR assay, which is recognized for determining histocompatibility, ***does not appear to be predictive of general immune responses in vivo***" (emphasis added- page 4 of the instant Office action). Applicants respectfully disagree.

Chapter 13 of the cited reference, Basic and Clinical Immunology (8^{th} ed.) shows many instances where MLR (or MLC and other related assays) are useful for determining immune

functions other than histocompatibility alone. For instance, on page 208, second column, paragraph 3, the article says" MLC may be used as a histocompatibility assay and as a test for immunocompetence of T cells, particularly in immunodeficiency disorders (see Chapters 20 and 21).

Applicants further point out that the MLR assay depends upon the interactions of T lymphocytes with other cells, in particular, with the stimulator cells used in the described MLR protocol. As explained in an excerpt from this textbook, T cells cooperate with antigen presenting cells (page 31, col. 2) *in vivo*. The most potent antigen presenting cells are dendritic cells, which are the predominant cell type found in the irradiated stimulator cell population, as explained in the Fong Declaration (see paragraphs 5-6). Thus the MLR assay does measure the interaction of T-lymphocytes with other cells, and therefore is a valid predictive model system for immune responses.

The Examiner also cites the reference Kahan (1991) for its statement that "no *in vitro* assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions," (page 5 of the instant Office action). The Examiner further cites Piccotti *et al.* (1999) to show that "IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result *in vitro* does not result in a measurable response *in vivo*" (page 5 of the instant Office action). The Examiner further cites Campo *et al.* (2001) and says "while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosupprepssive effects *in vivo*", (page 5 of the instant Office action).

Applicants respectfully disagree. Applicants submit that the Examiner has not correctly characterized the teachings of Kahan *et al.*, Picotti *et al.* and Campo *et al.* On the other hand, these references, in combination with those cited by Applicants, demonstrate that,the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomodulatory compounds.

For instance, the statement by Kahan *et al.* (see above) is inconsistent with what was known and accepted in the art at the time of filing regarding the MLR assay. For example, U.S. Patent No. 5,817,306 states, "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful

for treating graft versus host disease. **The results obtained from these assays are generally predictive of their *in vivo* effectiveness.**" (Column 12, lines 36-41; emphasis added). U.S. Patent No. 5,801,193, filed April 15, 1997, states that "[t]he **MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity.**" (Column 8, lines 8-10, emphasis added). U.S. Patent No. 5,648,376, filed January 19, 1995, states that "[a] measure of immunosuppression that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Column 11, lines 24-26). Therefore, Kahan's quoted statement contradicts well established scientific wisdom. As discussed extensively above, in fact, the MLR assay has been extensively used and is the best *in vitro* model for screening immunostimulatory agents. In fact, the examiner's cited reference, Picotti *et al.*, also supports this point, since the authors extensively used the MLC assay in their studies.

Picotti *et al.* studied the mechanism of alloimmune response and graft rejections. Picotti *et al.* in fact, confirms that "IL-12 is a key cytokine involved in promoting cell mediated immune responses in vivo" (page 1459, col. 1). Picotti *et al.* also showed that the IL-12R gamma subunit was critical for IL-12 driven enhanced alloimmune response ***in vitro* and *in vivo*** (see abstract). Based on their studies, one skilled in the art would know that immunostimulating compounds like IL-12 (or of this invention) could be used in immunoadjuvant therapy (with tumor-specific antibodies, which is also discussed in the Fong Declaration, Petersen *et al.* reference)for the treatment of tumors (cancer). One skilled in the art would know that immunostimulant molecules can be administered alone or together with other agents to stimulate T cell proliferation/ activation (immune function) ad therefore, one skilled in the art would know that such agents can be used to stimulate an antitumor response to a tumor antigen. If anything, Picotti *et al.*, supports the point that immunostimulants are useful for treating tumors.

Applicants respectfully point out that the Examiner has misinterpreted this statement, due to the fact that the authors refer to two different types of immunosuppressive effects. Campo *et al.* set out to look for an inhibitor of MHC *in vitro* which would have the fewest side effects *in vivo* (see Abstract). The authors note that high concentrations of zinc "impair **all** T cell and monocyte function" (page 20; emphasis added). The authors took this impairment as an indicator of toxicity, and therefore intentionally used concentrations of zinc below that at which all T-cell

function was impaired, in order to identify a concentration range that would not result in toxic effects. However, that does not mean that Campo *et al.* found zinc to have no immunosuppressive activity *in vivo*. In fact, the authors conclude, based upon their MLC results, that "zinc **could become an immunosuppressant in transplantation medicine** without toxic side effects" (page 21; emphasis added). Thus Campo *et al.* supports Applicants' position that those of skill in the art would interpret the results of MLC assays as having physiological relevance.

Applicants note that the Examiner has failed to point out several instances within these cited references wherein the authors stated that the MLR is an important method with a good predictive value. For example, Campo *et al.* teach that "the human mixed lymphocyte culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN-gamma, **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection ***in vivo***.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN-gamma **both *in vitro* and *in vivo***" (see page 18; emphasis added). Finally, Campo *et al.* teaches that "cyclosporin A, FK506, and other substances are used to prevent graft rejection. **In vitro experiments revealed an inhibition of the MLC**" (page 16). Thus the teachings of Campo *et al.* confirm that inhibition of the MLR is observed for known immunoinhibitory molecules, that are in actual clinical use.

Thus, while there are instances of unpredictability in some studies using the MLR assay, there are many more studies showing the usefulness and predictable results using MLR, as exemplified by the studies by Picotti, Landolfo and the IFN-gamma study and all the references submitted by the Applicants in this response. Therefore, the teachings within Basic and Clinical Immunology, Kahan *et al.*, Piccotti *et al.*, Campo *et al.*, in fact, support the usefulness of the MLR assay, and collectively show that **mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunomostimulatory compounds.**

The Examiner asserts that "without further guidance correlating the observed stimulatory activity to particular, useful property, it would require undue experimentation to use PRO335" (pages 9-10 of instant Office action). Applicants respectfully disagree.

Applicants respectfully submit that enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." The M.P.E.P. further explains that "If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." Applicants note that the specification clearly indicates that the claimed polypeptides are useful in the treatment of undesirable immune responses. The use of immunosuppressive molecules in the treatment of such disorders is well known in the art, as indicated by Kahan *et al.*, Picotti *et al.* and Campo *et al.*, made of record by the Examiner, as well as the references and U.S. Patents, discussed and made of record in the instantly filed IDS. Thus any further experimentation required for determining, for example, a particular dosage or method for the administration of PRO335 would not be considered undue.

Further, with respect to disclosure of the results of *in vitro* assays, the M.P.E.P. states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995)."

The M.P.E.P. also makes it clear that the burden of proof is on the Examiner, to demonstrate lack of correlation for an *in vitro* model. "(s)ince the initial burden is on the

examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example." A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka,* wherein the court stated that "based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

As discussed above, MLR was routinely used in the art to identify immunostimulants or immunosuppressors, and additionally, were found to have *in vivo* utility, in the treatment of various diseases and conditions. Further, the importance of immunostimulants in the treatment of cancer or in enhancing the effectiveness of previously identified treatments for cancer, including tumor-specific antibodies were well known in the art at the time of filing of the instant application, as discussed in several references cited above. For instance, costimulation of T cells inducing tumor regression and an antitumor response, both *in vitro* and *in vivo* was known (for e.g., Steinman *et al.* -submitted as Exhibit B with the Response filed October 25, 2004). Thus, one skilled in the art would know that immunostimulating compounds like IL-12 or PRO335 of this invention, could be useful in immunoadjuvant therapies, for the treatment of tumors (cancer) and could be administered either alone or together with other agents to stimulate T cell proliferation/ activation (immune function). These could be done without undue experimentation.

For the reasons given above, Applicants respectfully submit that the results of the MLR assay as shown in Example 74 of the present specification, provide a specific, substantial and credible utility under 35 U.S.C. §101 for the claimed invention.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 39-47 and 49-51 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

II. Rejections under 35 U.S.C. §112, first paragraph

Claims 39-43, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, allegedly as failing to comply with the written description requirement. The claims allegedly contain subject matter which was not described in the specification, at the time the application was filed, to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants respectfully disagree.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.

In *Environmental Designs, Ltd. v. Union Oil Co.*,, the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added). Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."

B. The Disclosure Provides Sufficient Written Description for the Claimed Invention

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO:290. The polypeptides comprising the sequence set forth in SEQ ID NO:290 meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of polypeptides with at least 80% sequence

identity to SEQ ID NO:290, which possess the functional property of being an immunostimulant in the MLR assay would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Applicants submit that, as discussed above, whether a specification shows that Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teachings provided by the specification. The inventor is not required to describe every single detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention is from the field of recombinant DNA technology. In addition, the claims recite that the polypeptide is an immunostimulant. It is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field. Accordingly, the teachings imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

Example 74 (page 208) of the present application provides step-by-step guidelines and protocols for the MLR assay. By following the disclosure in the specification, one skilled in the art could easily test whether a variant PRO335 polypeptide induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction. The specification further describes methods for the determination of percent identity between two amino acid sequences (page 67, line 34, to page 69, line 24 and Table 2 and 3, page 94-95). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 69, line 25, to page 72, line 34). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, pages 113-114). Accordingly, one of skill in the art could identify whether a variant PRO335 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 115, line 10, to page 117, line 9) and methods of preparing the PRO polypeptides.

Applicants have recited structural features, namely, 80% sequence identity to SEQ ID NO:290, which are common to the genus. Applicants have also provided guidance as to how to make the recited variants of SEQ ID NO:290, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

In view of the disclosure of the present application, a person skilled in the art would recognize that Applicants were in possession of the members of the genus which have the necessary common structural and functional attributes as described at the effective filing date of the present application. Thus the disclosed PRO335 polypeptide of SEQ ID NO: 290 is representative for a genus encompassing its variants.

In view of the above, Applicants respectfully request reconsideration and reversal of the written description rejection of Claims 39-43, 50 and 51 under 35 U.S.C. §112, first paragraph.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C46). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 30, 2006

(Panpan Gao 43,626)

Daphne Reddy
Reg. No. 53,507

on behalf of Daphne Reddy

HELLER EHRMAN, LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638